REMARKS

Rejections under 35 USC 112, first paragraph

Claims 1-4 and 16 are rejected as failing to provide written description.
The examiner states that method of claim 1 is directed to identification of diet-regulated disease-associated polynucleotides in *any life form*, and that "the specification has not been found to provide an adequate written description of any 'two different inbred known genotypes' as they occur in humans, much less any and all other life forms."

The examiner is respectfully directed to paragraphs 70-73 that generally describes using two inbred strains of mice and exposing them to different diets, and more specifically to paragraphs 83-94 that particularly describes the use of two inbred strains of mice (obese yellow A^{vy}/A and agouti A/a), one strain of which is susceptible to obesity, hyperinsulinemia, and mammary cancer.

Further, the examiner states that the specification "fails to provide adequate written description of how such genes, even if expressed differently, [are] in fact associated with a disease." (Office Action Para. 9). The applicant respectfully points out that the very aim of the invention is to identify such diet-regulated, disease associated genes, and that this is done by the method described in the specification and in claim 1. The method is based on statistically significant quantitative differences in disease susceptibility between two different genotypes (in this case, inbred mouse strains). Specifically, two different inbred genotypes are selected (A and B). One of these genotypes (A) is more susceptible to a disease (e.g., obese yellow $A^{vy}/$), and the other genotype (B) is less susceptible to the same disease (e.g., agouti A/a). Then each genotype is divided into two groups (A1 and A2 and B1 and B2). For one genotype, each group is fed a different diet (A1 is fed diet No.1 and A2 is fed diet No.2, and similarly for B1 and B2). Gene expression is then compared across the strains that differ in *either genotype or in diet, but not in both.* Thus A1 is compared with A2; A1 is compared with B1; but A1 is not compared with B2. (This answers the examiner's next question as to how various factors such as age, race

and sex are taken into account, as each experiment deals with only one variable at a time). Genes are identified that show significant changes in expression under these experimental conditions (e.g., a 2.0-fold or greater change in gene expression) and it is a premise of the experiment (and an inventor-defined term) that genes showing these characteristics are defined as being "diet-regulated, disease-associated genes." This is an eminently reasonable term since the genes that show such up- (or down-) regulation relative to the non-susceptible genotype, only show such characteristics in response to diet *in the disease-susceptible strain.*

The examiner states that the specification lacks adequate description of how factors such as race, age and sex are taken into account. The applicant respectfully draws examiner's attention to the above paragraph wherein the method is described clearly showing that the only variable being examined between the two species is diet and disease susceptibility. In all other respects, the individual subjects are the same.

The examiner suggests that the applicant is relying upon obviousness to satisfy the written description requirement (Office Action Paras. 10-11). The applicant respectfully and strongly denies this assertion and believes that the exemplary descriptions at paragraphs 70-73, paragraphs 83-94 and throughout the specification and in the claims are more than adequate to describe invention as required by 35 USC 112 and show that the applicant was in possession of the invention at the time of filing and to allow one of ordinary skill to practice the claimed invention.

Further, the Examiner suggests that the specification lacks written description because it does not provide the independently-derived QTLs to which the identified genes may be compared (Office Action Paras. 12-13). Firstly, the QTLs are not themselves part of the invention. Claim 1 does not even require a step of QTL comparison. QTLs are only used to further support the identification of the gene already identified by the method of claim 1. The QTLs have been previously identified by others and QTLs for various phenotypes are well known and easily available. Secondly, the specification does indeed describe a large number of exemplary QTLs in Fig 3. The applicant certainly is not suggesting that

the invention is to be practiced without guidance to particular materials such as QTLs as in the Hybritech case. The examples and the list of QTLs enable the invention and undue experimentation would not be necessary to practice the claimed invention.

In view of the above reasoning, it is respectfully requested that the present rejection under 35 USC 112 be withdrawn.

Rejections under 35 USC 112, first paragraph

Claims 1-4 and 16 are rejected as indefinite for use of the word "inbred" (Para 17) and also because of the use of the terms "more" or "less" when referring to disease susceptibility of two strains.

The term "inbred" is well understood in the art and is not indefinite. The International Committee on Standardized Nomenclature for Mice has ruled that a strain of mice can be considered "inbred" at generation F_{20} (See *Genetic Variants and Strains of the Laboratory Mouse, Committee on standardized genetic nomenclature for mice* (1989). Lyon, M. F. and Searle, A. G., eds. (Oxford University Press, Oxford), pp. 1-12).

To say that one genotype is more susceptible to a disease, and that another genotype is less susceptible to the same disease will generally have a clear meaning to one of skill in the art, as we tend to use strains of mice with great differences in disease susceptibility. But these are rarely if ever defined (for example: 30% +/- 5% at $p < 0.05$). This is because the specific susceptibility depends on the strain comparisons, and compiling such data is laborious, costly, and of little practical use. For example, in one of the exemplary embodiments discussed in the specification, one would have to compare C57BL/6 vs BALB/c, and BALB/c vs C3H, and C3H vs C57BL/6, etc...in fact there are about 30 strains commonly used in research, and about 150 that could be used. So the problems are obvious. Nonetheless, in order to advance prosecution and to make the claim clearer, the applicant has amended the claim to state that one genotype is more susceptible to a disease, and that another genotype is NOT susceptible to the same disease. The applicant

hopes and believes that such an amendment will remove any question of indefiniteness. Support for such an amendment can be found, for example, at paragraphs 54, 67, 70, and 90.

In view of the above reasoning, it is respectfully requested that the rejections be withdrawn.